**025 RADIATION DOSE FOR LOCAL CONTROL IN NON-HODGKIN LYMPHOMA: BRITISH NATIONAL LYMPHOMA INVESTIGATION RANDOMISED TRIAL.**

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**Introduction:** This multicentre randomised phase III trial was designed to investigate lower dose radiation schedules in non-Hodgkin lymphoma for both indolent (I-L) [24 Gy in 12 fractions] and aggressive (Ag-L) [30 Gy in 15 fractions] compared to a standard 40-45 Gy in 1.8 to 2 Gy fractions.

**Methods and materials:** Patients >18 yrs requiring radiotherapy for non-Hodgkin's lymphoma where the aim of treatment was local control were eligible. Randomisation was stratified by histological subtype. Central review of pathology was mandated and achieved in 85%. The primary endpoint was overall response rate (ORR) within the irradiated field and the study was powered to detect a 15% difference in ORR with a 90% power and 5% significance level.

**Results:** Between April 1997 and January 2005, there were 1001 randomisations from 40 centres; 361 I-L and 640 Ag-L. 81% received RT as part of primary radical treatment. Amongst the I-L 69% received RT alone for cure of localised disease and in Ag-L 80% had RT in a combined modality schedule with chemotherapy and 12% received RT alone for cure of localised disease. Compliance with the protocol treatment was >95%.

In the I-L group the 1 month ORR was 95% in the high dose (HD) arm and 92% in the low dose arm (LD) [Difference 3%, 95% CI -5% to 6%]; in the Ag-L arm the 1 month ORR was 92% in both arms [Difference 0% 95% CI -4.5% to 4.5%]. The complete response rates (CR) were 79% and 82% respectively [95% CI -8% to 6%] for I-L; 83% and 82% respectively [95% CI -6% to 8%] for Ag-L. At median follow up of 5.6 years, 5-year freedom from local progression (FFLP) rates for I-L are 78.8% (HD) and 75.6% (LD) [p=0.37], and in Ag-L 83.5% (HD) and 82.8% (LD) [p=0.66]. No significant differences in overall survival (OS) were seen. No difference is seen on subgroup analysis in those patients having radical treatment alone, those with aggressive lymphoma receiving consolidation RT after chemotherapy, or those who received rituximab as part of their induction chemotherapy. Acute and late toxicity was low in both arms; erythema in the irradiated field was reduced in the lower dose arms (29% vs. 41%; p=0.001).

**Conclusion:** There was no difference in ORR, FFLP or OS between the two dose levels tested; 24 Gy in I-L and 30 Gy in Ag-L. I-L lymphoma should be the standard of care.

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**026 SHOULD RADIATION THERAPY (XRT) BE THE STANDARD THERAPEUTIC APPROACH FOR STAGE I FOLLICULAR LYMPHOMA (FL)? A COMPARATIVE EFFECTIVENESS ANALYSIS OF THE NATIONAL LYMPHOCARE STUDY (NLCS).**

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**Aims:** Follicular lymphoma (WHO) grade I or II (FL) in early stage nodal disease can be treated effectively by radiotherapy alone. The extent of optimal target volumes remains controversial with a high rate of relapse (RLS) out-field after Involved field irradiation, but higher toxicity and potentially risks of secondary neoplasia after large field techniques. Therefore, this study aimed to determine adequate age-adapted irradiation volumes in FL patients (pts) (randomized trial (RDL)) and to evaluate standardized radiotherapy in elderly FL pts [prospective observation trial (OB)]

**Methods:** In FL stage I-I and limited stage III disease, pts up to 65 years (ys) were randomized to Extended field (EF) or Total lymphatic irradiation (TLI), basic dose 30 Gy, boost 10/14 Gy (lymphoma size dependent). Pts aged 66-75 ys were treated with EF, pts >75 ys with involved field (IF) radiotherapy.

**Results:** A total of qualified 255 pts were recruited. In the RD trial, 202 pts, median age 54 (23-65) ys, were randomized to EF or TNI. In the OLS trial pts, median age 70 (64-84) ys, were treated with EF (79%) or IF (21%). In the updated combined analysis of all 255 pts, overall survival is 95%, median observation period of 51 months. RLS and progression-free survival are 60% and 59% at five years with a plateau after six complete remissions. CRs were obtained in 92% of all pts. RLS occurred in 24% of all pts, median interval 24 months. In the RD pts, differences in RLS rates and probabilities between treatment arms emerge and the required number for unblinding will shortly be reached.

First RLS of all 255 pts were correlated with extent of radiotherapy: RLS developed predominantly as new manifestations (92%, 79% new site alone), more often out-of-field (73%), and were in 68% located on the opposing side of the diaphragm. RLS was mostly entirely nodal (76%), rarely bone marrow (8%), or extranodal (10%).

In 65% of all RLS, histology was obtained, revealing transition into secondary diffuse large B-cell lymphoma (DLBCL) in 30% of these pts (19% of all RLS, 5% of all study pts), 15 (7-96) months from diagnosis. Second tumors were observed as solid tumors (n=6), sarcoma and AML (one case each) and possibly MDS (n=2) after 36 (4-119) months.

**Conclusions:** In early stage nodal FL, standardized RT induced high rates of CR with excellent survival, and relapse is rare beyond six years. However, the predominance of relapse in new and out-of-field nodal sites is suggestive of early occult dissemination, warranting consideration in new treatment concepts.

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**027 FOLLICULAR LYMPHOMA: CURABILITY BY RADIOTHERAPY IN LIMITED STAGE NODAL DISEASE? UPDATED RESULTS OF A RANDOMIZED TRIAL.**

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**Aims:** Follicular lymphoma WHO grade I or II (FL) in early stage nodal disease can be treated effectively by radiotherapy alone. The extent of optimal target volumes remains controversial with a high rate of relapse (RLS) out-field after Involved field irradiation, but higher toxicity and potentially risks of secondary neoplasia after large field techniques. Therefore, this study aimed to determine adequate age-adapted irradiation volumes in FL patients (pts) (randomized trial (RDL)) and to evaluate standardized radiotherapy in elderly FL pts [prospective observation trial (OBS)].

**Methods:** In FL stage I-II and limited stage III disease, pts up to 65 years (ys) were randomized to Extended field (EF) or Total lymphatic irradiation (TLI), basic dose 30 Gy, boost 10/14 Gy (lymphoma size dependent). Pts aged 66-75 yrs were treated with EF, pts >75 yrs with involved field (IF) radiotherapy.

**Results:** A total of qualified 255 pts were recruited. In the RD trial, 202 pts, median age 54 (23-65) ys, were randomized to EF or TNI. In the OLS trial pts, median age 70 (64-84) ys, were treated with EF (79%) or IF (21%). In the updated combined analysis of all 255 pts, overall survival is 95%, median observation period of 51 months. RLS- and progression-free survival are 60% and 59% at five years with a plateau after six complete remissions. CRs were obtained in 92% of all pts. RLS occurred in 24% of all pts, median interval 24 months. In the RD pts, differences in RLS rates and probabilities between treatment arms emerge and the required number for unblinding will shortly be reached.

First RLS of all 255 pts were correlated with extent of radiotherapy: RLS developed predominantly as new manifestations (92%, 79% new site alone), more often out-of-field (73%), and were in 68% located on the opposing side of the diaphragm. RLS was mostly entirely nodal (76%), rarely bone marrow (8%), or extranodal (10%).

In 65% of all RLS, histology was obtained, revealing transition into secondary diffuse large B-cell lymphoma (DLBCL) in 30% of these pts (19% of all RLS, 5% of all study pts), 15 (7-96) months from diagnosis. Second tumors were observed as solid tumors (n=6), sarcoma and AML (one case each) and possibly MDS (n=2) after 36 (4-119) months.

**Conclusions:** In early stage nodal FL, standardized RT induced high rates of CR with excellent survival, and relapse is rare beyond six years. However, the predominance of relapse in new and out-of-field nodal sites is suggestive of early occult dissemination, warranting consideration in new treatment concepts.
Background: Since 2005, patients in British Columbia (BC) (with limited-stage DLBCL (stage I/II, no B-symptoms, mass < 10cm) have been treated according to a PET-based algorithm. Following 3 cycles of R-CHOP, PET/CT scan was performed and those having no evidence of disease on PET/CT scan received IFRT. Other patients received an additional cycle of R-CHOP, while PET-positive patients received IFRT. We present an update of this ongoing experience.

Patients and Methods: Using the BC Cancer Agency Lymphoid Cancer database we identified all patients with limited-stage DLBCL treated with this PET-based approach between Mar 2005 and June 2010. Patients with primary CNS, primary testicular and transformed lymphomas were excluded. Clinical characteristics of the 134 patients identified are as follows: median age, 64 yr (range 22-88); 57%; male; 57%; stage I; 43%; stage II; 3%; PS-1: 11%; elevated LDH; 51%, at least 1 extranodal site; 32%, mass size ≥ 2 cm. Stage-modified IPI risk score: 20%; 6%; 49%; 1%; 23%; 2%; 8-3; 4. Median follow-up is 30 mos (range 3-68).

Results: After 3 cycles of R-CHOP: PET-negative, 103 patients (77%); PET-positive, 30, (22%); PET-indeterminate, 1, (1%). Elevated serum LDH (p=0.02) and mass size ≥ 2 cm (p=0.001) were predictive of PET status, whereas stage-adjusted IPI was of borderline significance (p=0.08). Of the 103 PET-negative patients, 100 completed treatment with one additional cycle of R-CHOP, 2 received IFRT due to physician choice and 1 died of toxicity before receiving any more treatment. 7/103 PET-negative patients have relapsed (3 initially localized at original site, 2 local and distant, 2 distant only). 3/7 PET-negative relapses were delayed, occurring between 2.5-4 years post initial diagnosis. 29/30 PET-positive patients received IFRT, 1 patient received an additional cycle of R-CHOP alone due to concern about toxicity. 9/30 PET-positive patients for whom complete therapy with IFRT have a high rate of distant relapse. Alternative approaches may be warranted in this subgroup.

Conclusion: The majority of patients with limited-stage DLBCL will be PET-negative after 3 cycles of R-CHOP and have an excellent outcome following abbreviated R-CHOP alone, although delayed relapses have been observed. PET-positive patients who complete therapy with IFRT have a high rate of distant relapse. Alternative approaches may be warranted in this subgroup.

029 6-YEAR FOLLOW-UP OF THE MINT STUDY SUGGESTS A ROLE FOR Radiotherapy TO BULKY DISEASE.

Methods: Between 05/2000 and 10/2003 823 patients were recruited of whom 396 received CHOP-21, 361 CHOP-21, 34 MACOP-B, and 32 PMInCEBO with or without rituximab. Results: Toxicity, incidence of adverse events, severe adverse events and second neoplasms in the CHEMO and the R-CHEMO arms were not significantly different. After a median follow-up of 70 (0.03-117) months, R-CHEMO compared to CHEMO patients had increased 6-year event-free (74.0% vs. 55.7%; p<0.001), progression-free (79.9% vs 63.8%; p<0.001) and overall survival (89.8% vs 80.0%; p<0.001). In a multivariate analysis event-free survival was affected by the addition of rituximab (HR 0.49; p< 0.001, age-adjusted IPI (HR 1.73; p<0.001), and bulky disease (HR 1.43, p=0.004). Similar effects were observed for PFS and OS, dividing R-CHEMO patients into a very favorable (aIPI=0, no bulky) with a 100% OS after 6xR-CHOP-21 and a less favorable subgroup (aIPI=1 and/or bulky disease). Outcome of aIPI=1 patients with 6xR-CHEMO in MInT was similar to R-ACVBP and better than 8xR-CHOP in GELA’s LH03-2B trial (BLOOD 2010; 116 [21]: abstract #109), where no radiotherapy was given.

Conclusions: Addition of rituximab to a CHOP-like regimen results in a significant improvement of outcome in young patients with good-prognosis diffuse large B-cell lymphoma, with significant survival benefit maintained during a 6-year follow-up. The superiority of 6xR-CHOP-21 in MInT compared to 8xR-CHOP-21 in LH03-2B suggests that this might be true for radiotherapy to bulky disease, which was included in the MInT, but not in the LH03-2B trial. While reduction of treatment in a randomized study like the FLYER trial of the DSHNHL is justified for young patients with very favorable DLBCL, further progress, e.g. by dose densification (UNFOLDER trial of the DSHNHL) and/or dose escalation is still warranted for the less favorable subgroup. Comparison of aIPI=1 patients in MInT and LH03-2B underlines the need of a randomized trial to define the role of radiotherapy to bulky disease, which is addressed in the ongoing UNFOLDER trial of the DSHNHL. Supported by Roche, Deutsche Krebshilfe and KML.